Search Strategy

FILE 'USPATFULL' ENTERED AT 19:39:21 ON 12 JUN 2003

		E	ALLAWAY G P/IN
L1	16	S	E4
		E	LITWIN V M/IN
L2	8	S	E4
L3	1	S	L2 NOT L1
		E	MADDON P J/IN
L4	31	S	E4
L5	18	S	L4 NOT (L1 OR L2)
L6	24833	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L7	12893	S	L6 AND (FUSION OR ENTRY)
L8	358	S	L7 AND (MACROPHAGE-TROPIC OR PRIMARY ISOLATE?)
L9	316	S	L8 AND (INHIBITOR? OR ANTIVIRAL?)
L10	43	S	L9 AND (MACROPHAGE/CLM OR PRIMARY/CLM)

FILE 'WPIDS' ENTERED AT 19:46:39 ON 12 JUN 2003

		E	ALLAWAY G P/IN
L11	18	S	E3
		E	LITWIN V M/IN
L12	10	S	E3
		E	MADDON P J/IN
L13	34	S	E3
L14	20	S	L13 NOT (L11 OR L12)
L15	15382	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L16	959	S	L15 AND (FUSION OR ENTRY)
L17	17	S	L16 AND (MACROPHAGE-TROPIC OR PRIMARY ISOLATE?)

FILE 'MEDLINE' ENTERED AT 19:47:57 ON 12 JUN 2003

		E	ALLAWAY G P/AU
L18	22	S	E3 OR E4
		E	LITWIN V M/AU
L19	10	S	E1
		E	MADDON P J/AU
L20	38	S	E3 OR E4
L21	28	S	L20 NOT (L18 OR L19)
L22	131456	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L23	5185	S	L22 AND (FUSION OR ENTRY)
L24	287	S	L23 AND (MACROPHAGE-TROPIC OR PRIMARY ISOLATE?)
L25	119	S	L24 AND (INHIBIT? OR ANTIVIRAL?)

L1 ANSWER 13 OF 16 USPATFULL
2000:109525 Method for preventing HIV-1 infection of CD4.sup.+ cells.
Allaway, Graham P., Mohegan Lake, NY, United States
Litwin, Virginia M., Fayetteville, NY, United States
Maddon, Paul J., Elmsford, NY, United States
Olson, William C., Ossining, NY, United States
Progenics Pharmaceuticals, Inc., Tarrytown, NY, United States (U.S. corporation)
US 6107019 20000822
APPLICATION: US 1997-876078 19970613 (8)
PRIORITY: US 1996-19715P 19960614 (60)
US 1996-14532P 19960402 (60)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides methods for inhibiting fusion of HIV-1 to CD4.sup.+ cells which comprise contacting CD4.sup.+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4.sup.+ cells is inhibited. This invention also provides methods for inhibiting HIV-1 infection of CD4.sup.+ cells which comprise contacting CD4.sup.+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4.sup.+ cells is inhibited, thereby inhibiting the HIV-1 infection. This invention provides non-chemokine agents capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4.sup.+ cells. This invention also provides pharmaceutical compositions comprising an amount of the non-chemokine agent capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4.sup.+ cells effective to prevent fusion of HIV-1 to CD4.sup.+ cells and a pharmaceutically acceptable carrier.

CLM What is claimed is:
1. An in vitro method for determining whether an agent is capable of inhibiting HIV-1 infection of a CD4.sup.+ cell susceptible to HIV-1 infection comprising the steps of: (a) fixing a chemokine receptor on a solid matrix wherein the chemokine receptor is a co-receptor for HIV-1 infection; (b) contacting the fixed chemokine receptor with the agent under conditions permitting binding of the agent to the chemokine receptor; (c) removing any unbound agent; (d) contacting the resulting fixed chemokine receptor to which the agent is bound with a predetermined amount of gp120/CD4.sup.+ complex under conditions permitting binding of gp120/CD4 .sup.+ complex to the fixed chemokine receptor in the absence of the agent; (e) removing any unbound gp120/CD4.sup.+ complex; (f) measuring the amount of gp120/CD4.sup.+ complex bound to the fixed chemokine receptor; and (g) comparing the amount measured in step (f) with the amount measured in the absence of the agent, a decrease in the amount bound in the presence of the agent indicating that the agent is capable of inhibiting HIV-1 infection.

2. An in vitro method for determining whether an agent is capable of inhibuting HIV-1 infection of a CD4.sup.+ cell susceptible to HIV-1 infection comprising the steps: (a) fixing a chernokine receptor on a solid matrix wherein the chemokine receptor is a co-receptor for HIV-1 infection; (b) contacting the fixed chemokine receptor with the agent and a predetermined amount of gp120/CD4.sup.+ complex under conditions permitting binding of the gp120/CD4.sup.+ complex to the fixed chemokine receptor in the absence of the agent; (c) removing any unbound agent or unbound gp120/CD4.sup.+ complex or both; (d) measuring the amount of gp120/CD4.sup.+ complex bound to the fixed chemokine

receptor; and (e) comparing the amount measured in step (d) with the amount measured in the absence of the agent, a decrease in the amount bound in the presence of the agent indicating that the agent is capable of inhibiting HIV-1 infection.

3. An in vitro method for determining whether an agent is capable of inhibiting HIV-1 infection of a CD4.sup.+ cell susceptible to HIV-1 infection comprising steps of: (a) fixing a gp120/CD4.sup.+ complex on a solid matrix; (b) contacting the fixed gp120/CD4.sup.+ complex with the agent under conditions permitting the binding of the agent to the gp120/CD4.sup.+ complex; (c) removing any unbound agent; (d) contacting the resulting fixed gp120/CD4.sup.+ complex to which the agent is bcund with a predetermined amount of chemokine receptor, wherein the chemokine receptor is a co-receptor for HIV-1 infection, under conditions permitting binding of the chemokine receptor to the fixed the gp120/CD4.sup.+ complex in the absence of the agent; (e) removing any unbound chemokine receptor; (f) measuring the amount of chemokine receptor bound to the fixed gp120/CD4.sup.+ ; and (g) comparing the amount measured in step (f) with the amount measured in the absence of the agent, a decrease in the amount bound in the presence of the agent indicating that the agent is capable of inhibiting HIV-1 infection.

4. An in vitro method for determining whether an agent is capable of inhibiting HIV-1 infection of a CD4.sup.+ cell susceptible to HIV-1 infection comprising steps of: (a) fixing a gp120/CD4.sup.+ complex on a solid matrix: (b) contacting the fixed gp120/CD4.sup.+ complex with the agent and a predetermined amount of chemokine receptor, wherein the chemokine receptor is a co-receptor for HIV-1 infection, under co)nditions permitting binding of the chemokine receptor to the fixed gp120/CD4.sup.+ complex in the absence of the agent; (c) removing any unbound agent or any unbound chemokine receptor or both: (d) measuring the amount of chemorkine receptor bound to the fixed gp120/CD4.sup.+ ; and (e) comparing the amount measured in step (d) with the amount measured in the absence of the agent, a decrease in the amount bound in the presence of the agent indicating that the agent is capable of inhibiting HIV-1 infection.

5. The method of claim 1, 2, 3, or 4 wherein the CD4.sup.+ is a soluble CD4.sup.+.

6. The method of claim 1, 2, 3, or 4 wherein the chemokine receptor is expressed on a cell.

7. The method of claim 6 wherein the cell is a L1.2 cell.

8. The method of claim 1 or 2, wherein the gp120, CD4.sup.+ or both are labeled with a detectable marker.

9. The method of claim 3 or 4 wherein the chemokine receptor is labeled with a detectable marker.

10. The method of claim 1 or 2, wherein the gp120, CD4.sup.+ or both are labeled with biotin.

11. The method of claim 2 or 4 wherein the chemokine receptor is labeled with biotin.

12. The method of any one of claims 1, 2, 3, or 4, wherein the chemockine receptor is CCR5.

L1 ANSWER 11 OF 16 USPATFULL

2001:112032 Fluorescence resonance energy transfer screening assay for the identification of compounds that are capable of abrogating macrophage-tropic HIV-1 cell fusion.
Allaway, Graham P., Moreton Merseyside, United Kingdom
Litwin, Virginia M., Fayetteville, NY, United States
Maddon, Paul J., Elmsford, NY, United States
Progenics Pharmaceuticals, Inc., Tarrytown, NY, United States (U.S. corporation)
US 6261763 B1 20010717
WO 9641020 19961219
APPLICATION: US 1998-973601 19980316 (8)
WO 1996-US9894 19960607 19980316 PCT 371 date 19980316 PCT 102(e) date
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Previous studies of human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein-mediated membrane fusion have focused on laboratory-adapted T-lymphotropic strains of the virus. The goal of this application was to develop a novel screening assay to characterize membrane fusion mediated by a primary HIV-1 isolate in comparison with a laboratory-adapted strain. To this end, a novel fusion assay was developed on the basis of the principle of resonance energy transfer, using HeLa cells stably transfected with gp120/gp41 from the T-lymphotropic isolate HIV-1.sub.LA1 or the macrophage-tropic primary isolate HIV-1.sub.JR-FL. These cells fused with CD4.sup.+ target cell lines with a tropism mirroring that of infection by the two viruses. Of particular note, HeLa cells expressing HIV-1.sub.JR-FL gp120/gp41 fused only with PM1 cells, a clonal derivative of HUT 78, and not with other T-cell or macrophage cell lines. These results demonstrate that the envelope glycoproteins of these strains play a major role in mediating viral tropism. Despite significant differences exhibited by HIV-1.sub.JR-FL and HIV-1.sub.LAI in terms of tropism and sensitivity to neutralization by CD4-based proteins, the present study found that membrane fusion mediated by the envelope glycoproteins of these viruses had remarkably similar properties. In particular, the degree and kinetics of membrane fusion were similar, fusion occurred at neutral pH and was dependent on the presence of divalent cations. The claimed invention will facilitate the screening and identification of novel agents that are capable of inhibiting these interactions.

CLM What is claimed is:
1. A method for determining whether an agent is capable of specifically inhibiting (A) the fusion of a macrophage-tropic primary isolate of HIV-1 to a CD4.sup.+ cell susceptible to infection by a macrophage-tropic HIV-1 or (B) the fusion of a T cell-tropic isolate of HIV-1 to a cell susceptible to infection by a T cell tropic HIV-1, but not both, which comprises: (a) contacting (i) a first appropriate CD4.sup.+ cell, which is labeled with a first dye, with (ii) a cell expressing the HIV-1 envelope glycoprotein of the macrophage-tropic primary isolate of HIV-1 on its surface, which is labeled with a second dye, in the presence of an excess of the agent under conditions which would normally permit the fusion of the CD4.sup.+ cell to the cell expressing the HIV-1 envelope glycoprotein on its surface in the absence of the agent, the first and second dyes being selected so as to allow resonance energy transfer between the dyes; (b) exposing the result of step (a) to conditions which would result in resonance energy transfer if fusion has occurred; and (c) determining whether there is a reduction of resonance energy transfer, when compared with the resonance energy transfer in the absence of the agent; (d) contacting (i) a second appropriate CD4.sup.+ cell, which is labeled with a first dye, with (ii) a cell expressing the HIV-1 envelope glycoprotein of a T cell-tropic

isolate of HIV-1 on its surface, which is labeled with a second dye, in the presence of an excess of the agent under conditions which would normally permit the fusion of the CD4.sup.+ cell to the cell expressing the HIV-1 envelope glycoprotein on its surface in the absence of the agent, the first and second dyes being selected so as to allow resonance energy transfer between the dyes; (e) exposing the result of step (d) to conditions which would result in resonance energy transfer if fusion has occurred; and (f) determining whether there is a reduction of resonance energy transfer, when compared with the resonance energy transfer in the absence of the agent, wherein a decrease in transfer in step (c) but not step (f) indicates that the agent is capable of specifically inhibiting fusion of the macrophage-tropic primary isolate of HIV-1 to CD4.sup.+ cells and a decrease in transfer in step (f) but not step (c) indicates that the agent is capable of specifically inhibiting the fusion of a T cell-tropic isolate of HIV-1 to the CD4.sup.+ cells.

2. The method of claim 1, wherein the first appropriate CD4.sup.+ cell is a PM1 cell, a primary human T lymphocyte, or a primary human macrophage.

3. The method of claim 1, wherein the second appropriate CD4.sup.+ cell is a HeLa-CD4 cell, a primary human T lymphocyte, a human T cell line, PM1 cell, or a C8166 cell.

4. The method of claim 1, wherein in step (a) the cell expressing the HIV-1 envelope glycoprotein of the macrophage-tropic primary isolate is an HIV-1.sub.JR-FL gp120/gp41 HeLa cell.

5. The method of claim 1, wherein in step (d) the cell expressing the HIV-1 envelope glycoprotein of the T-cell-tropic of HIV-1 is an HIV-1.sub.LAI gp120/gp41 HeLa cell.

6. The method of claim 1 wherein the agent is not previously known.

7. The method of claim 1, wherein the first dye is a rhodamine moiety-containing molecule and the second dye is a fluorescein moiety-containing molecule.

8. The method of claim 7, wherein the rhodamine moiety-containing molecule is octadecyl rhodamine B chloride and the fluorescein moiety-containing molecule is fluorescein octadecyl ester.

9. The method of claim 1, wherein the first dye is a fluorescein moiety-containing molecule and the second dye is a rhodamine moiety-containing molecule.

L1 ANSWER 10 OF 16 USPATFULL
2001:218025 Compounds capable of inhibiting HIV-1 infection.
Litwin, Virginia M., Fayetteville, NY, United States
Allaway, Graham P., Cheshire, Great Britain
Maddon, Paul J., New York, NY, United States
Progenics Pharmaceuticals, Inc. (U.S. corporation)
US 2001046512 **A1** 20011129
APPLICATION: US 2001-891062 A1 20010625 (9)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides an antibody capable of specifically inhibiting the fusion of an HIV-1 envelope glycoprotein cell with an appropriate CD4.sup.+ cell without cross reacting with the HIV-1 envelope glycoprotein or CD4 and capable of inhibiting infection by one or more

strains so HIV-1. This antibody is then used to identify a molecule which is important for HIV infection. Different uses of the antibody and the molecule are described.

CLM What is claimed is:

1. An antibody capable of specifically inhibiting the fusion of an HIV-1 envelope glycoprotein cell with an appropriate CD4.sup.+ cell without cross reacting with the HIV-1 envelope glycoprotein or CD4 and capable of inhibiting infection by one or more strains of HIV-1.

2. A monoclonal antibody of claim i.

3. A hybridoma cell line producing the monoclonal antibody of claim 2.

4. A chimeric monoclonal antibody of claim 2.

5. A humanized monoclonal antibody of claim 4.

6. A human monoclonal antibody of claim 2.

7. A single chain antibody or an antigen binding antibody fragment of claim 2.

8. A monoclonal antibody capable of competitively inhibiting the binding of the monoclonal antibody of claim 2 to its target molecule.

9. The monoclonal antibody of claim 2, 4, 3, 6, 7, or 8 labelled with a detectable marker.

10. A monoclonal antibody of claim 9 wherein the detectable marker is a radioactive isotope, enzyme, dye or biotin.

11. A pharmaceutical composition comprising the complete or a portion of the monoclonal antibody of claim 2, 4, 5, 6, 7 or 8 and a pharmaceutically acceptable carrier.

12. A method of inhibiting HIV-1 infection in a subject comprising administering an effective amount of the pharmaceutical composition of claim 11 to the subject.

13. An isolated nucleic acid molecule encoding the complete or a portion of the light chain protein of the monoclonal antibody of claim 2, 4, 5, 6 or 8.

14. An isolated nucleic acid molecule encoding the complete of a portion of the heavy chain protein of the monoclonal antibody of claim 2, 4, 5, 6 or 8.

15. An isolated nucleic acid molecule encoding the single chain antibody of claim 7.

16. A vector comprising the nucleic acid molecule of claim 13, 14 or 15 operably linked to a promoter of RNA transcription.

17. A vector comprising the nucleic acid molecules of claims 13 and 14 each operably linked to a promoter of RNA transcription.

18. A host vector system comprising one or more vectors of claim 16 or 17 in a suitable host cell.

19. A host vector system of claim 18, wherein the suitable host cell is

selected from a group consisting of a bacterial cell, an insect cell, a yeast cell or a mammalian cell.

20. The molecule specifically recognized by nhe monoclonal antibody of claim 1.

21. A glycoloipd molecule of claim 20.

22. A polypeptide molecule of claim 20.

23. An isolated nucleic acid molecule encoding the complete or a portion of the polypeptide of claim 22.

24. A multichain polypeptide molecule comprising the polypeptide of claim 22.

25. A soluble protein comprising a portion of the polypep-ide of claim 22 or 24.

26. A pharmaceutical composition comprising an effective amount of the soluble protein of claim 25 to inhibit HIV-1 infection and a pharmaceutically acceptable carrier.

27. A method of inhibiting HIV-1 infection in a subject comprising administering an effective amount of the pharmaceutical composition of claim 26 to the subject.

28. An isolated nucleic acid molecule encoding the complete or a portion of a polypeptide of the multichain polypeptide molecule of claim 24.

29. A vector comprising the nucleic acid molecule of claim 23 or 28 operably linked to a promoter of RNA transcription.

30. A host vector system comprising the vector of claim 29 in a suitable host cell.

31. A host vector system of claim 30, wherein the suitable host cell is a selected from a group consisting of a bacterial cell, an insect cell, a yeast cell or a mammalian cell.

32. A method for identifying inhibitors of HIV-1 infection comprising steps of: (a) contacting an effective amount of a compound with a system which contains HIV-1 gp120, HIV-1 gp41 or a fragment thereof with the molecule of claim 20 under conditions permitting formation of a complex between HIV-1 gp120, HIV-1 gp41 or a fragment thereof and the molecule, so as to inhibit such formation; and (b) determining the amount of complex formed; and (c) comparing the amount determined in step (b) with the control which is without the addition of the compound, a decrease in the complex formation indicating that the compound is capable of inhibiting HIV-1 infection.

33. A method of claim 32, wherein the compound is not previously known.

34. The compound identified by claim 33.

35. A pharmaceutical composition comprising the compound identified by the method of claim 32 and a pharmaceutically acceptable carrier.

36. A method of inhibiting HIV-1 infection in a subject comprising administering an effective amount of the pharmaceutical composition of claim 35 to the subject.

37. A kit for identifying inhibitors of HIV-1 infection which comprises, in separate compartments: (a) purified HIV-1 gp120, HIV-1 gp41 or a fragment thereof; and (b) the molecule of claim 20.

38. A transgenio nonhuman animal which comprises an isolated DNA molecule encoding the molecule of claim 22 or 24.

39. The transgenic nonhuman animal of claim 38 further comprising an isolated DNA molecule encoding the full-length or portion of the CD4 molecule sufficient for binding the HIV-1 envelope glycoprotein.

L1 ANSWER 7 OF 16 USPATFULL
2002:24365 Method for preventing HIV-1 infection of CD4+ cells.
Allaway, Graham P., Mohegan Lake, NY, United States
Litwin, Virginia M., Fayetteville, NY, United States
Maddon, Paul J., Elmsford, NY, United States
Olson, William C., Ossining, NY, United States
Progenics Pharmaceuticals, Inc., Tarrytown, NY, United States (U.S. corporation)
US 6344545 B1 20020205
APPLICATION: US 1997-831823 19970402 (8)
PRIORITY: US 1996-19715P 19960614 (60)
US 1996-14532P 19960402 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides methods for inhibiting fusion of HIV-1 to CD4.sup.+ cells which comprise contacting CD.sup.4+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4.sup.+ cells is inhibited. This invention also provides methods for inhibiting HIV-1 infection of CD4.sup.+ cells which comprise contacting CD4.sup.+ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the CD4.sup.+ cells is inhibited, thereby inhibiting the HIV-1 infection. This invention provides non-chemokine agents capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4.sup.+ cells. This invention also provides pharmaceutical compositions comprising an amount of the non-chemokine agent capable of binding to the chemokine receptor and inhibiting fusion of HIV-1 to CD4.sup.+ cells effective to prevent fusion of HIV-1 to CD4.sup.+ cells and a pharmaceutically acceptable carrier.

CLM What is claimed is:
1. A method of inhibiting HIV-1 infection of a CD4+ cell which comprises contacting the CD4+ cell with an antibody or portion of an antibody capable of binding to a chemokine receptor on the surface of the CD4+ cell in an amount and under conditions such that fusion of HIV-1 or an HIV-1 infected cell to the CD4+ cell is inhibited, thereby inhibiting HIV-1 infection of the CD4+ cell.

2. The method of claim 1, wherein the chemokine receptor is a CCR5 chemokine receptor.

3. The method of claim 1, wherein the CD4+ cell is a PM-1 cell.

4. The method of claim 1, wherein the CD4+ cell is a primary CD4+ T-cell.

5. The method of claim 1, wherein the CD4+ cell is a PMBC cell.

6. The method of claim 1, wherein the antibody is a monoclonal antibody.

L18 ANSWER 12 OF 22 MEDLINE
93378778 Document Number: 93378778. PubMed ID: 8369162. Synergistic inhibition of HIV-1 envelope-mediated cell fusion by CD4-based molecules in combination with antibodies to gp120 or gp41. Allaway G P; Ryder A M; Beaudry G A; Maddon P J. (Progenics Pharmaceuticals, Inc., Tarrytown, New York 10591.) AIDS RESEARCH AND HUMAN RETROVIRUSES, (1993 Jul) 9 (7) 581-7. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB CD4-based molecules were tested in combination with HIV-1-neutralizing antibodies directed against the V3 loop of gp120 or against gp41, for inhibition of HIV-1 envelope-mediated cell fusion. A virus-free cell fusion assay was developed, using Chinese hamster ovary cells that stably express HIV-1 gp120/gp41. These cells were incubated with dilutions of CD4-based molecules, antibodies, or mixtures of both, then overlaid with C8166 CD4+ T cells. Syncytia were counted and the degree of inhibition of cell fusion was determined. Synergy, additivity, or antagonism was calculated by the combination index (CI) method. The CD4-based molecules included soluble human CD4 as well as fusion proteins composed of CD4 linked to human immunoglobulin gamma 1 or gamma 2 heavy chains. Combinations of CD4-based molecules and monoclonal or polyclonal anti-V3 loop antibodies were synergistic in blocking HIV-1 envelope-mediated cell fusion (CI = 0.21-0.91 at 95% inhibition). Synergy was also observed with combinations of the CD4-based molecules and a broadly neutralizing anti-gp41 monoclonal antibody (2F5) (CI = 0.29-0.65 at 95% inhibition). These results demonstrate that molecules inhibiting HIV attachment act synergistically with molecules inhibiting HIV-1 fusion. The results suggest that CD4-based therapeutics would be more effective in patients with naturally occurring anti-V3 loop or anti-gp41 antibodies. In addition, there may be an advantage in coadministering CD4-based molecules and antibodies that block fusion, especially broadly neutralizing anti-gp41 antibodies, as a combination therapy for HIV-1 infections.

L18 ANSWER 10 OF 22 MEDLINE
96013752 Document Number: 96013752. PubMed ID: 7474069. Cross-clade neutralization of primary isolates of human immunodeficiency virus type 1 by human monoclonal antibodies and tetrameric CD4-IgG. Trkola A; Pomales A B; Yuan H; Korber B; Maddon P J; Allaway G P; Katinger H; Barbas C F 3rd; Burton D R; Ho D D; +. (Aaron Diamond AIDS Research Center, New York University School of Medicine, New York 10016, USA.) JOURNAL OF VIROLOGY, (1995 Nov) 69 (11) 6609-17. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We have tested three human monoclonal antibodies (MAbs) IgG1b12, 2G12, and 2F5) to the envelope glycoproteins of human immunodeficiency virus type 1 (HIV-1), and a tetrameric CD4-IgG molecule (CD4-IgG2), for the ability to neutralize primary HIV-1 isolates from the genetic clades A through F and from group O. Each of the reagents broadly and potently neutralized B-clade isolates. The 2F5 MAb and the CD4-IgG2 molecule also neutralized strains from outside the B clade, with the same breadth and potency that they showed against B-clade strains. The other two MAbs were able to neutralize a significant proportion of strains from outside the B clade, although there was a reduction in their efficacy compared with their activity against B-clade isolates. Neutralization of isolates by 2F5 correlated with their possession of the LDKW motif in a segment of gp41 near the membrane-spanning domain. The other two MAbs and CD4-IgG2 recognize discontinuous binding sites on gp120, and so no comparison between genetic sequence and virus neutralization was possible. Our data show that a vaccine based on the induction of humoral immunity that is broadly active across the genetic clades is not possible if immunogens

that express the epitopes for MAbs such as 2F5, 2G12, and IgG1b12 in immunogenic configurations can be created. Furthermore, if the three MAbs and CD4-IgG2 produce clinical benefit in immunotherapeutic trials in the United States or Europe, they may also do so elsewhere in the world.

L18 ANSWER 6 OF 22 MEDLINE
96323171 Document Number: 96323171. PubMed ID: 8709277. Human immunodeficiency virus type 1 membrane fusion mediated by a laboratory-adapted strain and a primary isolate analyzed by resonance energy transfer. Litwin V; Nagashima K A; Ryder A M; Chang C H; Carver J M; Olson W C; Alizon M; Hasel K W; Maddon P J; Allaway G P. (Progenics Pharmaceuticals, Inc., Tarrytown, New York 10591, USA.) JOURNAL OF VIROLOGY, (1996 Sep) 70 (9) 6437-41. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Previous studies of human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein-mediated membrane fusion have focused on laboratory-adapted T-lymphotropic strains of the virus. The goal of this study was to characterize membrane fusion mediated by a primary HIV-1 isolate in comparison with a laboratory-adapted strain. To this end, a new fusion assay was developed on the basis of the principle of resonance energy transfer, using HeLa cells stably transfected with gp120/gp41 from the T-lymphotropic isolate HIV-1LA1 or the macrophage-tropic primary isolate HIV-1JR-FL. These cells fused with CD4+ target cell lines with a tropism mirroring that of infection by the two viruses. Of particular note, HeLa cells expressing HIV-1JR-FL gp120/gp41 fused only with PM1 cells, a clonal derivative of HUT 78, and not with other T-cell or macrophage cell lines. These results demonstrate that the envelope glycoproteins of these strains play a major role in mediating viral tropism. Despite significant differences exhibited by HIV-1JR-FL and HIV-1LAI in terms of tropism and sensitivity to neutralization by CD4-based proteins, the present study found that membrane fusion mediated by the envelope glycoproteins of these viruses had remarkably similar properties. In particular, the degree and kinetics of membrane fusion were similar, fusion occurred at neutral pH and was dependent on the presence of divalent cations. Inhibition of HIV-1JR-FL envelope glycoprotein-mediated membrane fusion by soluble CD4 and CD4-IgG2 occurred at concentrations similar to those required to neutralize this virus. Interestingly, higher concentrations of these agents were required to inhibit HIV-1LAI envelope glycoprotein-mediated membrane fusion, in contrast to the greater sensitivity of HIV-1LAI virions to neutralization by soluble CD4 and CD4-IgG2. This finding suggests that the mechanisms of fusion inhibition and neutralization of HIV-1 are distinct.

L18 ANSWER 3 OF 22 MEDLINE
1998087481 Document Number: 98087481. PubMed ID: 9427609. AMD3100, a small molecule inhibitor of HIV-1 entry via the CXCR4 co-receptor. Donzella G A; Schols D; Lin S W; Este J A; Nagashima K A; Maddon P J; Allaway G P; Sakmar T P; Henson G; De Clercq E; Moore J P. (The Aaron Diamond AIDS Research Center, The Rockefeller University, New York, New York 10016, USA.) NATURE MEDICINE, (1998 Jan) 4 (1) 72-7. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB The bicyclam AMD3100 (formula weight 830) blocks HIV-1 entry and membrane fusion via the CXCR4 co-receptor, but not via CCR5. AMD3100 prevents monoclonal antibody 12G5 from binding to CXCR4, but has no effect on binding of monoclonal antibody 2D7 to CCR5. It also inhibits binding of the CXC-chemokine, SDF-1alpha, to CXCR4 and subsequent signal transduction, but does not itself cause signaling and has no effect on RANTES signaling via CCR5. Thus, AMD3100 prevents CXCR4 functioning as

both a HIV-1 co-receptor and a CXC-chemokine receptor. Development of small molecule inhibitors of HIV-1 entry is feasible.

L10 ANSWER 2 OF 2 MEDLINE

96004667 Document Number: 96004667. PubMed ID: 7568061. Fusogenic selectivity of the envelope glycoprotein is a major determinant of **human immunodeficiency virus** type 1 tropism for CD4+ T-cell lines vs. primary macrophages. Broder C C; Berger E A. (Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Sep 12) 92 (19) 9004-8. Journal code: 7505876.

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AB We investigated the relationship between the fusion selectivity of the envelope glycoprotein (env) and the tropism of different **human immunodeficiency virus** type 1 (**HIV**-1) isolates for CD4+ human T-cell lines vs. primary macrophages. Recombinant vaccinia viruses were prepared encoding the envs from several well-characterized **HIV**-1 isolates with distinct cytotropisms. Cells expressing the recombinant envs were mixed with various CD4+ partner cell types; cell fusion was monitored by a quantitative reporter gene assay and by syncytia formation. With CD4+ continuous cell lines as partners (T-cell lines, HeLa cells expressing recombinant CD4), efficient fusion occurred with the envs from T-cell line-tropic isolates (IIIB, LAV, SF2, and **RF**) but not with the envs from **macrophage-tropic** isolates (JR-FL, SF162, ADA, and Ba-L). The opposite selectivity pattern was observed with primary macrophages as cell partners; stronger fusion occurred with the envs from the **macrophage-tropic** than from the T-cell line-tropic isolates. All the envs showed fusion activity with peripheral blood mononuclear cells as partners, consistent with the ability of this cell population to support replication of all the corresponding **HIV**-1 isolates. These fusion selectivities were maintained irrespective of the cell type used to express env, thereby excluding a role for differential host cell modification. We conclude that the intrinsic fusion selectivity of env plays a major role in the tropism of a **HIV**-1 isolate for infection of CD4+ T-cell lines vs. primary macrophages, presumably by determining the selectivity of virus entry and cell fusion.